REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. All previously pending claims are cancelled and replaced with two new claims 18 and 19, which define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 3-6, 11, 14 and 16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is made moot by the cancellation of the rejected claims without prejudice.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

New claims 18 and 19, added to replace the previously pending claims, do not contain the homology language. New claim 18 is directed to a "variant", an isolated interferon-gamma production inducing protein which is different in amino acid sequence from the protein having the amino acid sequence of SEQ ID NO:2. Support for new claim 18 is found in the present

specification at page 9, second full paragraph, at page 15, lines 3-6 and in the paragraph bridging pages 15 and 16.

Claim 11 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the cancellation of claim 11 without prejudice. The new claims are not subject to this rejection.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 3-6, 11, 14 and 16 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while enabling for claims limited in scope to the IGIF of SEQ ID NO:2, and a specific variant of said protein which has an amino acid sequence of SEQ ID NO:2 where residue 70 is methionine or threonine, does not reasonably provide enablement for claims to a variant as defined in the claims. This rejection is obviated by the cancellation of the rejected claims without prejudice. This rejection as it may relate to new claims 18 and 19 is discussed below.

A person of skill in the art would have easily understood how to obtain the claimed "variant" based on the disclosures at page 9, last paragraph to page 13, first paragraph, and would have easily obtained such a "variant". That

is to say, the claimed "variant" can be easily obtained by applying recombinant DNA techniques, well known to public at the time the present application was filed, to the amino acid sequence of SEQ ID NO:2 disclosed in the present specification so as to prepare various variants having the amino acid sequence of SEQ ID NO:2 in which one or more amino acids are deleted, replaced or added; screening them in accordance with the screening method disclosed at page 14, second paragraph of the specification (i.e. screening variants by testing if they have interferon-gamma production inducing activity on immunocompetent cells) to select the "variants" having interferon-gamma production inducing activity; and then confirming the activity of the selected "variants" by administering them into mouse or rat. The process mentioned above would have been routine for a person of skill in the art at the time the present application was filed, even though the process would have taken some time. However, the process mentioned above certainly would not require any undue experimentation.

Furthermore, it should be noted that new claim 18 does not claim all of the variants of SEQ ID NO:2, it claims only a variant which is capable of inducing interferon-gamma production when administered into mouse and rat. The phrase in new claim 18 "said protein inducing IFN-gamma production when administered to

mouse and rat" has been introduced in place of the limitation "at least 90% homologous to the amino acid sequence of SEQ ID NO:2", which was considered by the examiner to be new matter. The new limitation "said protein inducing IFN-gamma production when administered to mouse and rat", which is supported by the disclosure at page 15, lines 3-6, limits the scope of the claimed invention to the variants that are close to mouse IL-18 and substantially to the variants having "at least 90% homologous to the amino acid sequence of SEQ ID NO:2".

In addition, applicants believe that one of skill in the art can easily obtain a variant having "at least 90% homologous to the amino acid sequence of SEQ ID NO:2" based on the disclosure of the present specification, even if no example of the variant having "at least 90% homologous to the amino acid sequence of SEQ ID NO:2", such as rat IL-18 (rat IL-18 has homology more than 90% to mouse IL-18 as evidenced by the copy of "ENDOGEN Recombinant Rat IL-18 Homology Table" from Pierce attached hereto), is not disclosed in the present specification. Since the method of preparing IL-18 from mouse liver without using recombinant techniques is disclosed in the specification in Experiment 1 (see pages 21-23 of the specification), applicants believe that one of skill in the art can also easily obtain IL-18

from rat liver, especially since mouse and rat both belong to the same family.

Also attached hereto are copies of the Endogen "Recombinant Human IL-1β Homology Table", "Recombinant Equine IL-2 Homology Table", "Recombinant Mouse IL-4 Homology Table ", "Recombinant Human IL-6 Homology Table ", and "Recombinant Porcine IL-12p70 Homology Table" from Pierce, and "The Cytokine Handbook", second edition, ACADEMIC PRESS LIMITED, pages 57-59 and 224-228, (1994). As shown in the attached documents, various mouse interleukins have much higher homology to the corresponding rat interleukins than to the corresponding interleukins from other mammals. Accordingly, applicants believe that one of skill in the art can easily obtain rat IL-18 based on the example of mouse IL-18 disclosed in the specification.

New claims 18 and 19 are enabled by the specification particularly in view of the high level of skill in the art and the wealth of knowledge in the art on making variants.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 3-9, 11, 14 and 16 remain rejected under 35 USC 102(b) as being anticipated by Nakamura et al. (Infect. Immun. 61:64-70, 1993) (Nakamura's first publication). The examiner still considers that the "factor" disclosed in Nakamura's first

publication is the same as the polypeptide of the present invention in view of Nakamura's later publication (Infect. Immun. 63:3966-3972, 1995). This rejection is obviated by the cancellation of the rejected claims without prejudice. The rejection as it may relate to new claims 18 and 19 is discussed below.

It should be noted that Nakamura did not succeed in isolating mouse IGIF at the time Nakamura's first publication was published. Please also note that the factor in Nakamura's first publication reveals plural bands on SDS-PAGE (see Figure 2 of Nakamura's first publication) and therefore is not a purified substance. Such an unpurified substance cannot be considered to be an isolated protein.

Furthermore, Nakamura's first publication teaches at page 68, right column, lines 23-28:

> Alternatively, a small fragment might have been lost during the purification procedures. The molecular shape may also have influenced the result. Since the factor lost its activity in SDS-PAGE, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor.

Nakamura's first publication clearly teaches that the factor having a molecular weight of 50-55 kDa comprises "a small fragment" having a smaller molecular weight than the factor,

and that they failed to confirm that "a small fragment" has an activity (i.e., IFN-gamma production inducing activity), because the factor lost its activity on SDS-PAGE. In this regard, it is believed that the factor disclosed in Nakamura's first publication is a complex of mouse IGIF and "a small fragment", and that mouse IGIF was not isolated in Nakamura's first publication, even if the factor in Nakamura's first publication comprises mouse IL-18, which was isolated in Nakamura's later publication.

The fact that mouse IGIF was not isolated in Nakamura's first publication means that even the presence of mouse IGIF was not confirmed in Nakamura's first publication. It is further apparent that the factor disclosed in Nakamura's first publication is different from an isolated protein as defined in new claim 18 in its homogeneity and purity, and that they are not the same substance.

Furthermore, new claim 18 is not directed to a natural mouse IGIF as disclosed in Nakamura's later publication, but rather is directed to an isolated protein which has an amino acid sequence different from the natural mouse IGIF sequence of SEQ ID NO:2. Therefore, the factor disclosed in Nakamura's first publication cannot anticipate the isolated protein new claim 18.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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